Hereditary Hemochromatosis: 2013

Fredric D. Gordon, M.D.
Director of Hepatology
Medical Director of Liver Transplantation
Lahey Clinic Medical Center
Burlington, MA

Agenda

• Iron overload syndromes
  – Hereditary hemochromatosis
• Genetics of hereditary hemochromatosis
• Normal and abnormal iron metabolism
• Diagnosis
• Treatment

Iron Overload Syndromes

• History of Hemochromatosis
  – 1865 – Trosier – first case
  – 1889 – von Recklinghausen – hemochromatosis
  – 1935 – Sheldon – inherited defect in iron metabolism
  – 1994 – Menzler Genetics – HFE
  – 1997 – present
  • DMT-1
  • Ferroportin
  • Transferrin receptor-2
  • Hemojuvelin
  • Hepcidin
Hereditary Hemochromatosis

- Mendelian genetics
  - Adult gamete
  - Zygote

Autosomal recessive inheritance

Primary Iron Overload Syndromes

- Hereditary Hemochromatosis
  - HFE-related
    - C282Y/H63D
    - C282Y/S65C
    - Other HFE mutations
  - Non-HFE-related
    - Hemojuvelin (HJV)
    - Transferrin receptor-2 (TfR-2)
    - Ferroportin (SLC40A1)
    - Hepcidin (HAMP)
    - African iron overload

Secondary Causes of Iron Overload

- Iron-loading anemias
  - Thalassemia major
  - Sideroblastic Anemia
  - Chronic Hemolytic Anemia
- Aplastic anemia
- Pyruvate kinase deficiency

- Parenteral
  - Transfusion
  - Iron dextran injection
  - Long term hemodialysis

- Chronic Liver Disease
  - Hepatitis B/C
  - Alcoholic liver disease
  - NASH
  - Porphyria Cutanea Tarda
  - Post Portocaval Shunting

- Miscellaneous
  - Neonatal Iron Overload
  - Accumulator syndromes
  - Congenital Atransferrinemia
Iron Overload Syndromes

- Patients with iron overload
  - 85% to 90% are C282Y/C282Y
  - Elevated transferrin saturation, ferritin
  - Periportal distribution of iron in parenchymal cells
  - Can progress to cirrhosis, diabetes, skin pigmentation, hepatocellular carcinoma

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<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>No. of Patients</th>
<th>C282Y n (%), H63D n (%), Wild type n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feder, et al.</td>
<td>USA</td>
<td>178</td>
<td>148 (83), 8 (4), 1 (0.5)</td>
</tr>
<tr>
<td>Beutler, et al.</td>
<td>USA</td>
<td>147</td>
<td>121 (82), 8 (5), 2 (1)</td>
</tr>
<tr>
<td>Jouanolle, et al.</td>
<td>France</td>
<td>65</td>
<td>59 (91), 3 (5), 0</td>
</tr>
<tr>
<td>Jazwinksa, et al.</td>
<td>Australia</td>
<td>112*</td>
<td>112 (100), 0, 0</td>
</tr>
<tr>
<td>Carella, et al.</td>
<td>Italy</td>
<td>75</td>
<td>48 (64), 2 (2.27), 2 (2.8)</td>
</tr>
<tr>
<td>Adams and Chakrabarti</td>
<td>Canada</td>
<td>128</td>
<td>122 (95), 2 (1.6), 2 (1.5)</td>
</tr>
<tr>
<td>Bacon, et al</td>
<td>USA</td>
<td>66</td>
<td>60 (91), 1 (1.5), 1 (0.5)</td>
</tr>
</tbody>
</table>

*All patients had a family history of iron overload
**Compound heterozygote

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Quantiative analysis of iron overload

<table>
<thead>
<tr>
<th>Population</th>
<th>Country</th>
<th>Prevalence of homozygous C282Y with normal ferritin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary care</td>
<td>USA</td>
<td>1 in 270</td>
</tr>
<tr>
<td>Gen’l public</td>
<td>Norway</td>
<td>1 in 220</td>
</tr>
<tr>
<td>Primary care</td>
<td>N. America</td>
<td>1 in 333</td>
</tr>
<tr>
<td>Gen’l public</td>
<td>Australia</td>
<td>1 in 146</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1 in 240</td>
</tr>
</tbody>
</table>

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Iron Overload Syndromes

- Families of probands
  - HFE mutation analysis has replaced HLA-typing
  - HFE mutation analysis, TS and ferritin
  - For analysis of risk in children – perform mutation analysis in spouse (or other parent) first
  - May be able to avoid testing in children


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HFE-Related Hereditary Hemochromatosis, a Multistep, Multifactorial Iron-Overload Disorder


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Normal Iron Homeostasis in Humans

**Slide 13**

**Spectrum of Iron Disorders**

- **Anemia of chronic disease**
  - Insufficient iron made available for hematopoiesis

- **Hemochromatosis**
  - Iron deposition liver, endocrine organs, heart & skin

*Courtesy of Ed Morris, MD*

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**PO iron**

- Duodenal enterocyte
- Fe
- Ferroportin
- Transferrin
- Hepatocyte (Fe storage reservoir)
- Transport of Fe to bone marrow for Hb production
- Transferrin receptor

- Balance maintained by regulation of absorption & distribution
- No physiological excretion method

*Normal*

*Courtesy of Ed Morris, MD*

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**PO iron**

- Duodenal enterocyte
- Fe
- Ferroportin
- Transferrin
- Macrophage
- RBC
- Hepatocyte (Fe storage reservoir)
- Transport of Fe to bone marrow for Hb production
- Transferrin receptor

*Normal*

*Courtesy of Ed Morris, MD*
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- **Hepcidin**
  - Produced by hepatocytes
  - Iron metabolism hormone

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- **Normal Fe Transport**
  - Fe uptake → Fe release into plasma
  - Fe exporting cells:
    - Duodenal enterocyte
    - Macrophage
    - Hepatocyte

**Slide 18**

- **Hepcidin-influenced Fe Transport**
  - Fe uptake → Fe retained
  - Fe exporting cells:
    - Duodenal enterocyte
    - Macrophage
    - Hepatocyte

*Courtesy of Ed Morris, MD*
Hepcidin

- Increased production:
  - Inflammation (IL-6 driven)

- Decreased production:
  - Anemia
  - Hypoxia
  - Hemochromatosis

PO iron
Duodenal enterocyte
Fe
Ferroportin
Transferrin
Macrophage
RBC
Hepatocyte
(Fe storage reservoir)

Increased Hepcidin

- Inflammation

PO iron
Duodenal enterocyte
Fe
Ferroportin
Transferrin
Macrophage
RBC
Hepatocyte
(Fe storage reservoir)

Hepcidin

- Increased production:
  - Inflammation (IL-6 driven)

- Decreased production:
  - Anemia
  - Hypoxia
  - Hemochromatosis
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PO iron
Duodenal enterocyte
Fe
Ferroportin
Transferrin
Macrophage
RBC
Hepatocyte
(Fe storage reservoir)
Hepcidin
Decreased Hepcidin
• Hemochromatosis
• Anemia
• Hypoxia

Courtesy of Ed Morris, MD

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Hereditary Hemochromatosis - Diagnosis

Requirements of Diagnosis
• Suspicion, serum iron studies
• Genetic test
• Differential diagnosis
  – Alcoholic liver disease
  – Chronic viral hepatitis
  – Nonalcoholic steatohepatitis
• Liver biopsy
• Use of Hepatic Iron Index

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Hemochromatosis – clinical approach

• Frequently present with non-specific symptoms:
  – Unexplained arthropathies
  – Impotence
  – Hyperpigmentation
  – Liver dysfunction
  – Diabetes
  – Cardiomyopathy
**Slide 25**

**Typical Symptoms in Patients with HH**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness, lethargy, fatigue</td>
<td>40-85</td>
</tr>
<tr>
<td>Apathy, lack of interest</td>
<td>40-85</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>30-60</td>
</tr>
<tr>
<td>Weight loss</td>
<td>30-60</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>40-60</td>
</tr>
<tr>
<td>Loss of libido, impotence</td>
<td>30-60</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>20-60</td>
</tr>
<tr>
<td>Congestive heart failure symptoms</td>
<td>0-40</td>
</tr>
</tbody>
</table>

**Slide 26**

**Common Physical Findings in HH**

<table>
<thead>
<tr>
<th>Finding</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatomegaly</td>
<td>60-85</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>50-95</td>
</tr>
<tr>
<td>Skin pigmentation</td>
<td>40-80</td>
</tr>
<tr>
<td>Arthritis (second, third metacarpophalangeal joints)</td>
<td>40-60</td>
</tr>
<tr>
<td>Clinical diabetes</td>
<td>10-60</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>10-40</td>
</tr>
<tr>
<td>Loss of body hair</td>
<td>10-30</td>
</tr>
<tr>
<td>Testicular atrophy</td>
<td>10-90</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>0-30</td>
</tr>
</tbody>
</table>
Hereditary Hemochromatosis

Symptoms and Physical Findings (%)

- No symptoms 73
- Lethargy, and/or weakness 25
- Loss of libido, impotence 12
- Arthralgias 13
- Diabetes 5
- Skin pigmentation 5

Am J Gastroenterol 92:784-789, 1997

Evaluation of Iron Stores

- Serum iron, TF saturation and ferritin
- Liver biopsy for stainable iron, biochemical determination of iron
- Noninvasive imaging modalities
  - Computed tomography
  - Magnetic resonance imaging
  - Magnetic susceptibility
- Iron removed by phlebotomy (1 U=250 mg)
Iron Warehouse

Iron in Blood

Blood Iron Studies in HH

Normal | HH
---|---
Serum iron (µg/dl) | 50-150 | 180-300
Transferrin (mg/dl) | 250-370 | 200-300
Transferrin saturation (%) | 20-50 | 80-100
Serum ferritin (ng/ml) | Males | 20-300 | 500-6,000
                  | Females | 15-250 | 500-6,000

Iron studies

Serum Iron
- Very variable - diurnal variation
- Not very useful for assessing iron stores

Low Result:
- Diurnal
- Intercurrent illness
- Chronic disease

High Result:
- Diurnal
- Iron overload
- Iron therapy

Courtesy of Ed Morris, MD
Iron studies

Transferrin
- Iron transport molecule
- Deposits iron in any cell expressing transferrin receptors

<table>
<thead>
<tr>
<th>Low result</th>
<th>High result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic disease</td>
<td>Iron deficiency</td>
</tr>
</tbody>
</table>

Transferrin Saturation
- Suggests the amount of iron being actively transported

<table>
<thead>
<tr>
<th>Low result</th>
<th>High result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency/Chronic disease</td>
<td>Iron overload</td>
</tr>
</tbody>
</table>

Ferritin
- Reasonable reflection of body stores
- Acute phase protein
- Synthesized in the liver

<table>
<thead>
<tr>
<th>Low result</th>
<th>High result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>Acute phase</td>
</tr>
</tbody>
</table>

Source: Courtesy of Ed Morris, MD
Role of Liver Biopsy

- Less important since HFE testing
- Primary purpose is to identify advanced fibrosis
  - Screening for HCC
  - EGD screening for varices
- High risk for advanced fibrosis
  - C282Y homozygotes with ferritin>1000 (20-45%)
  - Excessive alcohol
  - Elevated liver enzymes

Role of Liver Biopsy

- Secondary purpose – diagnosis
  - Elevated iron studies or elevated liver enzymes
  - Lack C282Y homozygosity
    - No HFE mutation
    - Compound heterozygote
- Hepatic iron index
  - Hepatic iron concentration / age
    - > 1.9
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**Cirrhosis Rates**

<table>
<thead>
<tr>
<th>Ferr &gt;1000</th>
<th>↑AST or ALT</th>
<th>Plt &lt;200K</th>
<th>Excess EtOH</th>
<th>Cirrhosis Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>20-45</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>&gt;80</td>
</tr>
</tbody>
</table>


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**Population Screening**

**Optimal Characteristics**

- Common
- Easy to diagnose
- Non-invasive diagnosis
- Non-diagnosis = morbidity/mortality
- Treatment available

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**Iron Overload Syndromes**

- Population screening for hemochromatosis
  - 41,038 adults screened in San Diego
  - Health appraisal unit
  - CBC, transferrin saturation, ferritin level, HFE genotype
  - Questionnaire

Iron Overload Syndromes

• Population screening for hemochromatosis
  – 152 C282Y/C282Y
  – 616 C282Y/H63D
  – 67% of C282Y/C282Y had elevated ferritin
  – No difference in symptoms from controls
  – 1 of 152 with signs and symptoms of hemochromatosis

  – ? Value of screening

Beutler et al., Lancet 359:211-218, 2002

Iron Overload Syndromes

• Population screening for hemochromatosis/iron overload
  – HEIRS trial
  – 99,711 participants screened in 5 North American sites
  – Multi-ethnic primary care population

Adams et al., NEJM 352:1769-1778, 2005

<table>
<thead>
<tr>
<th>Race or Ethnic Group</th>
<th>Total No. of Participants</th>
<th>C282Y/C282Y</th>
<th>C282Y/H63D</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>44,582</td>
<td>281</td>
<td>0.64</td>
</tr>
<tr>
<td>Native American</td>
<td>648</td>
<td>1</td>
<td>0.15</td>
</tr>
<tr>
<td>Hispanic</td>
<td>12,459</td>
<td>7</td>
<td>0.027</td>
</tr>
<tr>
<td>Black</td>
<td>27,124</td>
<td>4</td>
<td>0.014</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>698</td>
<td>0</td>
<td>0.012</td>
</tr>
<tr>
<td>Asian</td>
<td>12,772</td>
<td>0</td>
<td>0.000039</td>
</tr>
<tr>
<td>Multiple/unknown</td>
<td>1,928</td>
<td>6</td>
<td>-</td>
</tr>
</tbody>
</table>

Adams et al., NEJM 352:1769-1778, 2005
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Management

Phlebotomy

- If Ferritin >1000 - need to remove up to 25g Fe

  - 500ml blood contains 250mg Fe
  - 1 unit = 100 units

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Management

Phlebotomy

- Induction Phase
  - Usually weekly
  - 1-2 units
  - Ensure Hct >34-35%
  - Check ferritin:
    - Every 12 weeks until <50

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Hereditary Hemochromatosis

Response to Therapy

Management

Phlebotomy

- Maintenance frequency finding phase
  - Stop weekly phlebotomies
  - Check ferritin once a month
  - Trigger phlebotomy when ferritin > 50
  - After 12 months, count number of phlebotomies per year

Management

Phlebotomy

- Maintenance
  - Goal is to keep ferritin 50-100
  - Usually required q1-4 months
  - Check ferritin twice a year
  - 'Catch up' phlebotomies as needed

Management

Diet

- Realistically little role
- Avoid large quantities Vitamin C
  - Increased Fe absorption
  - Increases Fe release from storage sites
  - Rare reports of inducing lethal cardiac failure
**Management**

**Other options**

- **Chelation**
  - Can remove approx. 25 mg Fe per day (500 ml blood 250 mg)
  - Less than a weekly phlebotomy

- **Desferoxamine (Desferal)**
  - 8-12 hour infusions 5 days/week
  - Optic effects

**Future perspectives**

- **Hepcidin assay**
  - Only available in research laboratories

- **?? Hepcidin replacement therapy**
Results of Therapy

- Reduction to normal tissue iron stores.
- Improved survival if diagnosis and treatment before development of cirrhosis and diabetes.
- Improved sense of well-being, energy level.
- Improved cardiac function.
- Improved control of diabetes.
- Reduction in abdominal pain.
- Reduction in skin pigmentation.
- Normalization of elevated liver enzymes.
- Resolution of hepatic steatosis (approximately 50% of cases).
- No reversal of established cirrhosis.
- Reduction in portal hypertension in cirrhosis.
- No improvement in arthropathy.
- No reversal of testicular atrophy.
Hereditary Hemochromatosis: Survival


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Hereditary Hemochromatosis: Survival with Cirrhosis


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Conclusions

- Hereditary hemochromatosis is a common condition
- Diagnosis requires suspicion
- New tools for accurate and early diagnosis
- Successful treatment options